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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,317	07/22/2003	Nikolay Korokhov	D6471	1681

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EXAMINER	
SCHLAPKOHL, WALTER	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,317	KOROKHOV ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	MAIL

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7-10,12,13 and 15-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7-10,12,13 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 9/27/2006 in which claims 4, 11, 14, 19 and 20 were cancelled and claims 1, 3, 5, 7-10, 12-13 and 15-18 were amended. Claims 1, 3, 5, 7-10, 12-13 and 15-18 are pending and under examination in the instant Office action.

Any rejection recited in the last Office action not set forth herein is hereby WITHDRAWN.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/27/2006 has been entered.

Claim Objections

Claims 3 and 10 are objected to because of the following informalities: claims 3 and 10 comprise non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5, 10 & 13, and therefore dependent claims 7 & 8, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. **These are new rejections which are, in part, necessitated by amendment.**

Claim 1 recites "[a] recombinant adenovirus vector, comprising (i) a gene encoding a heterologous protein; (ii) a wild-type Ad5 fiber protein comprising an immunoglobulin-binding domain of Staphylococcus aureus Protein A; and (iii) a gene encoding a fusion protein comprising a targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of anti-human CD40 antibody and an

immunoglobulin Fc domain" in lines 1-8 (emphasis added). Claim 1 is vague and indefinite in that it is unclear whether Applicant intends that the fusion protein of part (iii) comprises a targeting ligand selected from the group consisting of 1) CD40 ligand, 2) a single change fragment (scFv) of anti-human CD40 and 3) an immunoglobulin Fc domain; or whether Applicant intends a fusion protein comprising an immunoglobulin Fc domain and a targeting ligand wherein the targeting ligand is either a CD40 ligand or a single chain fragment (scFv) of anti-human CD40 antibody.

Claim 3 recites "[t]he adenovirus vector of claim 1, wherein said immunoglobulin-binding domain is inserted at the HI loop or the carboxy terminal of said fiber protein" in lines 1-3 (emphasis added). Claim 3 is vague and indefinite in that the metes and bounds of the phrase term "carboxy terminal of said fiber protein" is unclear. Does Applicant intend such a vector wherein the immunoglobulin binding domain is inserted anywhere in the carboxyl terminal portion of the fiber protein (e.g., somewhere in the carboxyl terminal half of the protein), or does Applicant intend such a vector wherein the immunoglobulin binding domain is inserted at the carboxyl terminus of said fiber protein?

Similarly, claims 5, 10 and 13 recite immunoglobulin-binding domains inserted at the "carboxy terminal" of either a fiber protein or a fiber-fibritin chimera. Does Applicant intend such a vector wherein the immunoglobulin binding domain is inserted anywhere the carboxyl terminal portion of the fiber/fiber-fibritin protein (e.g., somewhere in the carboxyl terminal half of the protein), or does Applicant intend such a vector wherein the immunoglobulin binding domain is inserted at the carboxyl terminus of said fiber/fiber-fibritin protein?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 7-10, 12-13 and 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record**

but has been modified in order to accommodate Applicant's amendment(s).

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to any recombinant adenovirus vector wherein a fiber protein comprising an immunoglobulin-binding domain binds to an immunoglobulin (Ig) Fc domain fused to a CD40L or single chain fragment (scFv) of anti-human CD40 targeting ligand which in turn binds to a cell surface CD40 molecule. The claims encompass any adenovirus with (i) a gene encoding a heterologous protein, (ii) a modified fiber protein (any modification from any adenovirus) comprising an immunoglobulin-binding domain (including antibodies and other large proteins that contain Ig domains), and (iii) a gene encoding a fusion protein comprising a CD40 targeting ligand selected from CD40L and a single chain fragment of anti-human CD40 and an immunoglobulin Fc domain. Some claims are limited to a recombinant adenovirus vector comprising (i) a gene

encoding heterologous protein; (ii) a wild-type Ad5 fiber protein comprising an immunoglobulin-binding domain of Staphylococcus aureus Protein A; and (iii) a gene encoding a fusion protein comprising an immunoglobulin Fc domain and either a CD40 ligand or a single chain fragment (scFv) of anit-human CD40 antibody. Some claims are further limited to such viruses wherein the fiber protein is a fiber-fibritin chimera.

The nature of the subject is complex because, in order for targeting to occur, the fiber protein modification must be made in such a way as to allow for functional display of the immunoglobulin-binding domain on the surface of the virus. The Fc domain-ligand fusion protein must also be expressed at amounts abundant enough to allow for a complex to form between it and the virus and the cell surface molecule. Even should the appropriate amount of expression of the soluble Fc domain-ligand fusion molecule be reached, it would have to be secreted with the proper timing and abundance so as to allow for an Ad-Fc binding-domain::Fc-ligand::surface molecule complex to form. Without enough of the Fc-ligand fusion molecule present, the native tropism of the adenovirus would not be inhibited. This is especially problematic in vivo where presence of the natural viral fiber knob would drive Ad(5) vectors to the liver and

other cells/tissues that express the Coxsackievirus and Adenovirus receptor (CAR).

Breadth of the claims: The claims are very broad in that they encompass *any* recombinant adenovirus with (i) with *any* gene encoding a heterologous protein, *any* modified fiber protein comprising an any immunoglobulin-binding domain or *any protein* containing an immunoglobulin-binding domain, and/or (iii) *any* fusion protein comprising one of the recited CD40 targeting ligands. The complex nature of the subject matter is exacerbated by the breadth of the claims.

State of the art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for *in vivo* adenovirus targeting. Even a review of the state of the art post-filing (Mizuguchi et al, *Human Gene Therapy* **15**:1034-1044, 2004; of record) concedes that "when systemically administered, vector dissemination, resulting in accumulation in liver, is unavoidable" (page 1037, second paragraph). Mizuguchi also notes that to create a strictly targeted Ad vector, two basic requirements must be met: construction of vectors that abolish natural viral tropism and identification and incorporation of a foreign ligand with high affinity for a specific cellular receptor *into the capsid of the Ad vector*. Furthermore, in an

article published post-filing by a group that includes the instant inventors (Korokhov et al. *Journal of Virology* **77**(24):12931-12940, 2003; of record), Korokhov et al teach that adapter-mediated targeting requires the production and purification of at least two different components (the virus and the targeting ligand), their subsequent conjugation in a targeting complex, and the purification of that complex from non-reacted components (page 12935). Thus, the claimed recombinant Ad would have to be purified, complexed with the Fc-targeting ligand fusion protein and then purified again before *in vivo* targeting could be achieved.

With regard to a modified fiber protein containing an immunoglobulin binding domain, Everts et al teach that modified Ad fiber proteins must include some essential elements such as a fiber tail for incorporation into the capsid and a trimerization motif to maintain the prerequisite trimeric structure for successful virion assembly (Everts et al. *Current Gene Therapy* **4**:337-346, 2004; of record). Everts et al also describe modified fiber proteins with knob deletions and chimeric fiber proteins and note that not all targeting ligands are compatible with fiber trimerization (page 342). In particular, Everts et al note that the intracellular reducing environment is not compatible with disulfide bond formation and hence correct

protein folding. Everts et al also teach that there is a size limitation of peptides that can be inserted into the C-terminus of the Ad fiber protein before trimerization is inhibited, wherein, in one case, 27 amino acids was found to be above the limit.

Finally, as of the effective filing date, there is no art of record for the successful genetic re-targeting of an Ad vector comprising a genetically modified fiber protein used in conjunction with an adapter molecule produced by the same Ad vector, either *in vivo* or *in vitro*.

Predictability of the art: The area of the invention is unpredictable. As discussed above, the method of Ad targeting is highly complex and unpredictable. Indeed, it requires ablation of the natural viral tropism of the Ad vector as well as incorporation of a foreign ligand with high affinity for a specific cellular receptor *into the capsid of the Ad vector*.

Guidance of the specification and existence of working examples: The specification teaches that targeting ligands incorporating a human Fc domain and either an anti-CD40 single chain antibody or CD40L form stable complexes with Ad vectors with fiber proteins comprising an insert of the immunoglobulin-binding domain (C domain, Cd) of *Staphylococcus aureus* Protein A. The 59 amino acid-long Cd was inserted into both the HI loop

and at the C terminus of the AD5 wild type fiber protein via a linker sequence. Although the specification notes that this insertion did not affect the yield or growth dynamics that might be expected by incorporation of such a large domain into this site, it does not teach what structural or chemical properties allow for the insertion of large immunoglobulin-binding domains other than that of the C domain of Protein A. (To that end, Applicant has described a method for screening fiber-C domain species that can be employed for use in their targeted Ad vector.)

Neither does the specification teach how to make and use any modified fiber protein with an immunoglobulin-binding domain. The only other modified fiber protein taught by the specification is a fiber-fibritin chimera (page 28), but the specification provides little or no guidance with regard to other fiber modifications that are encompassed by the claims and little to no guidance on where immunoglobulin-binding domain insertions within such modified fibers would be tolerated or should be made.

The specification also provides little or no guidance on the kinds of Ad vectors which can be targeted in this manner. Applicant states that the high degree of structural similarity of the Ad fiber knob domains from different serotypes predicts

the compatibility of the Protein A C domain with the frameworks of fiber knobs other that that of Ad5 (page 18), but the specification provides little or no guidance on where the gene encoding the Fc-targeting ligand should be inserted in other Ad serotypes or how such serotypes might be used to successfully target the cells of interest and how to do so without unwanted side effects, such as vector-associated immunogenic effects.

The specification includes five examples of Ad vectors with fiber proteins containing the C domain of *S. aureus* and one example of an Ad vector with and Fc-targeting ligand molecule but the specification does not have one example of the claimed targeted recombinant adenovirus vector comprising both of these elements (plus a heterologous gene).

Perhaps most importantly, the specification does not make up for the deficiencies in the art that allow for successful targeting of any of the claimed vectors *in vivo*. Neither of the two basic requirements for targeting of an adenovirus described above have been met, i.e. the specification does not teach a single adenovirus vector wherein the native tropism has been ablated and wherein the targeting ligand with specific high affinity for the cellular receptor has been incorporated into the capsid of the virus. Because the specification does not

teach how to use this vector in any other manner, the claimed adenovirus is therefore not enabled.

Amount of experimentation necessary: The quantity of experimentation necessary to make the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use the targeted adenovirus vector commensurate in scope with the claims. In order to determine how to successfully target an adenovirus vector comprising the claimed elements, one of skill in the art would first have to make the adenovirus in such a way as to meet or overcome the requirements for targeting, i.e. ablate the native tropism of the virus and incorporate the targeting ligand with high affinity for the cell surface molecule into the viral capsid. Otherwise, one would have to determine how to produce and secrete sufficient amounts of the Fc-targeting ligand molecule in such a manner as to complex with all exposed, modified fiber proteins to prevent CAR-association and re-target the Ad vector to the proper cell(s). Furthermore, the skilled artisan would have to determine which other immunoglobulin-binding domains are compatible with which Ad fiber proteins, modified or otherwise. The skilled artisan would also have to determine where such immunoglobulin-binding domain insertions could be tolerated without disrupting modified fiber protein

trimerization. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

In view of the lack of guidance provided by the specification as well as the nature of the invention and the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1, 3, 5, 7-10, 12-13 and 15-18 are not considered enabled by the instant specification.

Claims 9-10, 12-13 and 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record.**

The claims are drawn toward a recombinant adenovirus vector, comprising (i) a gene encoding a heterologous protein, (ii) a modified fiber protein comprising an immunoglobulin-

binding domain, and (iii) a gene encoding a fusion protein comprising a targeting ligand and an immunoglobulin Fc domain, wherein binding of said immunoglobulin-binding domain to said Fc domain connects the targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of anti-human CD40 antibody. The claims encompass *any* recombinant adenovirus vector, *any* modified fiber protein with *any* immunoglobulin-binding domain, and/or a gene encoding *any* fusion protein comprising any immunoglobulin Fc domain and any CD40 ligand or single chain fragment (scFv) of anti-human CD40 antibody. Some claims are further limited to such vectors wherein the fiber protein is a fiber-fibritin chimera or wherein the fiber protein comprises an immunoglobulin binding domain of Staphylococcus aureus Protein A.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation and any combination thereof. The specification describes five examples of Ad vectors with fiber proteins containing the C domain of *S. aureus* and one example of an Ad

vector with and Fc-targeting ligand fusion molecule, but the specification does not describe one example of the claimed targeted recombinant adenovirus vector comprising both of these elements (plus a heterologous gene).

The prior art is silent with respect to adenoviral vectors which comprise the recited components such that modified fiber protein is capable of trimerization and such that the virion is capable of assembly. Belousova et al (cited above; IDS Ref. AF) teach that as of Applicant's filing date, "all Ad targeting endeavors have been limited to attempts to engraft short peptide ligands into the rather complex framework of the fiber knob, with no efforts being made to expand the repertoire of ligand candidates beyond peptides. As a result of the limited availability of high-affinity peptide ligands suitable for incorporation into the Ad fiber, only a few genetically targeted Ad prototypes have been derived" (see page 8622, 1st column, 2nd full paragraph). Belousova et al showed that inserts ranging in size from 13 to 83 amino acids could be tolerated, but this finding was for inserts placed within the HI loop of the Ad5 fiber protein, not at the carboxyl terminus (see, e.g., page 8629, 1st column, 1st full paragraph).

Even if one accepts that the specification teaches in general terms how to make a very small subgroup of vectors with

one or two examples of a modified fiber protein comprising an immunoglobulin-binding domain, a gene encoding a Fc-ligand fusion protein, and a heterologous gene, the specification does not describe how to make any adenoviral vector comprising such components such that the virion is capable of being assembled properly and thus propagated.

Given the very large genus of nucleic acid molecules encompassed by the rejected claims, and given the lack of description provided by the prior art and specification with regard to the sequences capable of targeting a recombinant adenoviral vector, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of Ad vectors capable of targeting to a cell surface molecule. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those Ad vectors that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 9-10, 12-13 and 15-18.

Response to Arguments

Applicant argues that the recitation of "targeted" in claims 3, 5, 7, 8, 10 and 12-18 and the "wherein" clause of claims 1 and 9 have been deleted, although Applicant asserts that the amendments were not made for the purposes of patentability with the meaning of 35 U.S.C. §§§§101, 102, 103 or 112.

Applicant's arguments have been carefully considered and are respectfully found unpersuasive. Examiner notes for the record that the "targeted" language has not been completely removed from the claims in that, e.g., claim 1 still recites an adenovirus vector comprising a "targeting ligand" in line 4. Applicant's arguments are not persuasive because the specification does not teach how to make and use this vector in any other manner except for targeting to CD40+ cells; therefore the claimed adenovirus is not enabled.

Conclusion

No claim is allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax

telephone number for the Group is (571) 273-8300. Note: If Applicant does submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should

be directed to Walter A. Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office.)

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

November 27, 2006

NANCY VOGEL
PRIMARY EXAMINER